The following remarks address the substance of the Office Action of November 5, 2001:

I. Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has rejected Claims 31-36 and 39 under 35 U.S.C. § 112, first paragraph on the assertion that the specification does not enable to one of skill in the art to practice the claimed invention. Specifically, the Examiner asserts that it is unclear if polypeptides of the claimed invention function as antigens, whether they are recognized by patient sera, whether antibodies against the claimed polypeptides would inhibit Factor VIII function, and whether administration of the peptides could block function of the antibodies against Factor VIII. In support of this assertion, the Examiner cites two documents by Van Regenmortel (Methods: A Companion to Methods in Enzymology 9, p. 465-472 (1996)) and Palmer et al. (Vox Sanguinis 1997, 72:148-161).

Submitted herewith is a Declaration accompanied by Exhibits A-C demonstrating that the specification as filed is fully enabling for the claimed invention. The Declaration and Exhibits provide proof that the claimed polypeptides are in fact antigenic and that antibodies directed against the claimed polypeptides are found in human serum. In addition, the accompanying Declaration and Exhibits demonstrate that antibodies against some of the claimed polypeptides inhibit Factor VIII activity. Please note that in view of the fact that the faxed Declaration may be difficult for the Examiner to read, Applicants have provided a printout of the unsigned Declaration for the Examiner's convenience.

The Examiner stated that it is unclear whether the linear polypeptides would be antigenic and states that that Van Regenmortel notes that the fact that "about 90% of antibodies raised against intact proteins do not react with any peptide fragment derived from the parent protein is taken as an indication that all these antibodies are directed to discontinuous epitopes." (page 466, column 1). It is true that the epitopes of the present invention are linear (continuous) epitopes, as evidenced by their sequences in Paragraph 4 of the attached Declaration. However, as stated in Paragraphs 5 and 6 of the Declaration, linear epitopes consisting of amino acids 1652-1664, 1681-1696, and 1794-1815 were in fact able to elicit antibodies in immunized rabbits and these antibodies bound to the peptides used in the immunization. This demonstrates that

linear polypeptides are in fact antigenic. Paragraph 6 of the Declaration also reveals that, in a plasma pool of approximately 4800 donors, natural antibodies were detected which bound to the linear epitopes consisting of amino acids 1652-1664, 1681-1696, and 1794-1815. Therefore, the experiments disclosed in the Declaration reveal that antibodies are directed to linear (continuous) epitopes.

Further, although Van Regenmortel expresses concern that linear epitopes may not be antigenic, in fact, he appreciates on page 466, column 1 that antibodies elicited from short peptides (i.e. linear peptides) "are of considerable practical importance since they have many applications as immunological reagents in diagnostics and gene product detection as well as being the active component in synthetic vaccines." Therefore, even Van Regenmortel appreciated the value of linear antigens.

The Examiner also cited Palmer et al., who used synthetic peptide arrays to identify novel Factor VIII inhibitor epitopes. Palmer et al. noted that each patient pattern of anti-factor VIII antibody reactivity appears to be polyclonal, directed against multiple sites located within the amino and carboxyl terminus of the protein and seems to be unique for each plasma investigated (page 156, col 2). In addition, Palmer et al. noted that it is difficult to predict the importance that any given antibody-epitope interaction may have on Factor VIII coagulation activity based on the results of synthetic peptide assays alone (page 157, col 2).

However, Palmer et al. did not identify peptides having a high probability of antigenicity. Rather Palmer simply screened a number of contiguous peptides within Factor VIII. In particular, Palmer et al. used only sequential fragments from 20-960 and 1411-2351 of FVIII (page 149, col 2) to conduct their assays, with each synthetic peptide containing eleven amino acids. In contrast to the peptides of Palmer, as discussed in the accompanying Declaration and Exhibits, the present peptides were pre-screened to identify those having a high probability of strong antigenicity. In particular the present peptides were identified by searching surface regions characterized by a high hydrophilicity, flexibility, accessibility and high probability of an outer location.

The Examiner questioned whether administration of the peptides could be used to block inhibition of FVIII activity by antibodies directed against Factor VIII. As

indicated in the accompanying Declaration and Exhibits, antibodies against Factor VIII fragments consisting amino acids 1652-1664, 1681-1696, and 1794-1815 inhibited Factor VIII activity, thus indicating that these fragments can prevent inhibition of Factor VIII activity by antibodies.

In view of the above arguments, Applicants respectfully request the withdrawal of the rejection to Claims 31-36 and 39 under 35 U.S.C. § 112, first paragraph.

II. Rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected Claims 31, 33-36, and 39 under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention.

The Examiner has rejected Claims 31, 33-36, and 39 as being indefinite and ambiguous in the recitation of the various polypeptide sequences, since the sequence of A3 of Factor VIII is not found in the specification as filed. The sequence of A3 of Factor VIII is well known in the literature, and one of skill in the art can easily find this sequence in the literature. In fact, Applicants referred to the disclosure of this sequence in the Verhar reference cited on page 10, lines 18-21 in the specification as filed, and again on page 11, lines 21-23. Thus, those skilled in the art are familiar with the sequence of Factor VIII.

Claim 33 has been amended to recite "An" before "antigenic" and to recite that the claimed polypeptides comprise a tyrosine or a histidine residue contained in the polypeptides of Claim 31.

Claims 34, 36 and 39 have been amended to address the concerns of the Examiner. Specifically, Claims 34, 36 and 39 have been amended to incorporate the phrase "antigenic polypeptide amino acid sequence" in reference to the claimed epitopes (Claim 32) and fragments (Claims 36 and 39). Claims 31, 32 and 35 have been amended to clarify the invention. Support for these claim amendments are found within the specification as filed.

In light of the above arguments, Applicants respectfully request the withdrawal of the rejection to Claims 31-36 and 39 under 35 U.S.C. § 112, second paragraph.

III. Rejection under 35 U.S.C. § 102(b) over Capon et al.

The Examiner has rejected Claims 31-33, 36 and 39 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,965,199 (Capon et al.). The Examiner asserts that the cited '199 Patent teaches the antigenic polypeptides of Claim 31 as well as teaches fusion or carrier proteins of the Factor VIII peptides which are linked to the Factor VIII peptide and which could include either tyrosine or histidine linked to the peptide as recited in Claim 39 and Claim 33, respectively, of the present invention, and further teaches a pharmaceutical composition comprising a peptide of Factor VIII and an acceptable pharmaceutical vehicle, thereby anticipating the claimed invention.

However, the claimed peptides of the invention, as recited in Claim 31 contain Factor VIII fragments containing amino acids 1652-1696, 1739-1831, and 1885-1917 of the A3 domain of Factor VIII as described in Verhar et al. (Nature, Vol. 312, p. 339 (1984)). Epitopes within those regions are outlined further in Claim 32. Paragraph 4 of the accompanying Declaration reveals how these peptides and epitopes were selected.

The disclosed Factor VIII fragments of the invention are not taught in the cited '199 reference. The Examiner cites Figure 10 (described in column 8, lines 23-53) of '199 as anticipating the antigenic peptides of the invention. Column 8, lines 23-53 of '199 describes Figure 10 as a complete sequence of overlapping clones deduced from Capon et al. The reference discloses in column 39, line 48 through column 40, line 30, that polypeptides consisting of amino acids 1799-1860 (61 amino acids), 1000-1096 (97 amino acids), and 710-885 (176 amino acids) were injected into rabbits to confirm that the cloned sequence did encoded Factor VIII. However, the '199 patent does not teach the Factor VIII fragments claimed herein which were identified by the present inventors as containing an antigenic site.

However, the '199 reference does not disclose or teach the claimed Factor VIII fragments. It does not disclose the fragments of Factor VIII as recited in Claim 31 nor does it disclose the epitopes of the A3 domain recited in Claim 32. Further, it does not teach conformational epitopes as found in Claims 34 and 35.

In view of the above arguments, Applicants respectfully request the withdrawal of the rejection to Claims 31-33, 36 and 39 under 35 U.S.C. § 102(b).

IV. Conclusion

In view of the foregoing amendments, remarks and accompanying Declaration, Applicants respectfully assert that the present application is fully in condition for allowance. If any issues remain that may be addressed by a phone conversation, the Examiner is invited to contact the undersigned at the phone number listed below.

The changes made to claims by the current amendment, including insertions and **[deletions]**, are shown on an attached sheet entitled **VERSION WITH MARKINGS TO SHOW CHANGES MADE**, which follows the signature page of this amendment. No new matter has been added herewith.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: May 6, 2002

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

The following paragraph and heading have been added on page 1, immediately following the Title of the Invention:

Cross-Reference to Related Applications

This application is the U.S. National Phase under 35 U.S.C. §371 of International Application PCT/BE95/00068, filed July 14, 1995, which claims priority of Belgian application BE 9400666, filed July 14, 1994, the disclosures of which are incorporated herein by reference in their entireties.

The sentence on page 16, lines 3 and 4, has been amended as follows:

- the epitope contained between aspartic acid **[2018]**2108 and glycine 2121, defined by the following sequence:

The paragraph on page 17, lines 15 to 19, has been amended as follows:

These characteristics are particularly pronounced in the cases of epitopes SEQ ID No: 2 and SEQ**[P]** ID No: 5, which comprise sequences which are relatively "long" in amino acids, i.e. comprise 16 and 22 amino acids, respectively.

In the Claims:

31. **(Amended)** An antigenic polypeptide comprising**[of]** at least 7 amino acids **[of the polypeptide sequence A3]** of a **[factor]**Factor VIII fragment**[, having an amino acid sequence]** selected from the group consisting of a **[sequence]**Factor VIII fragment contained between arginine 1652 and arginine 1696 inclusive, a **[sequence]**Factor VIII fragment contained between threonine 1739 and aspartic acid 1831 inclusive, and a **[sequence]**Factor VIII fragment contained between glutamic acid 1885 and arginine 1917 inclusive.

32. **(Amended)** An antigenic polypeptide according to Claim 31, **[having]**wherein said Factor VIII fragment comprises an epitope selected from the group consisting of:

[the epitope]a Factor VIII fragment contained between arginine 1652 and tyrosine 1664 (SEQ ID No:1), **[the epitope]**a Factor VIII fragment contained between aspartic acid 1681 and arginine 1696 (SEQ ID No:2), **[the epitope]**a Factor VIII fragment contained between threonine 1739 and tyrosine 1748 (SEQ ID No:3), **[the epitope]**a Factor VIII fragment contained between asparagine 1777 and phenylalanine 1785 (SEQ ID No:4), **[the epitope]**a Factor VIII fragment contained between glutamic acid 1794 and tyrosine 1815 (SEQ ID No:5), **[the epitope]**a Factor VIII fragment contained between methionine 1823 and aspartic acid 1831 (SEQ ID No:6), **[the epitope]**a Factor VIII fragment contained between glutamic acid 1885 and phenylalanine 1891 (SEQ ID No:7), **[the epitope]**a Factor VIII fragment contained between glutamic acid 1893 and alanine 1901 (SEQ ID No:8), and **[the epitope]**a Factor VIII fragment contained between aspartic acid 1909 and arginine 1917 (SEQ ID No:9).

33. **(Amended)** An antigenic polypeptide according to Claim 31, **[containing at least either]**wherein said antigenic polypeptide comprises tyrosine or histidine**[linked]**.

34. **(Amended)** A conformational epitope containing at least two different epitopes of the antigenic polypeptide of Claim 32.

36. **(Amended)** A complex comprising a carrier protein or a carrier peptide linked to the antigenic polypeptide amino acid sequence fragment of Claim 31 or the conformational epitope of Claim 35.

39. **(Twice Amended)** A pharmaceutical composition comprising at least the antigenic polypeptide **[fragment]** of Claim 31, or the conformational epitope of Claim 35 and an acceptable pharmaceutical vehicle.